Original article

Hypomagnesemia in hemodialysis patients taking proton pump inhibitors

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ABSTRACT

Background: Proton pump inhibitors (PPIs) are in routine widely prescribed to hemodialysis patients. Recent studies have reported the association of PPIs use with hypomagnesemia in patients with long term hemodialysis. This study aims to determine the frequency of hypomagnesemia in patients of hemodialysis taking proton pump inhibitors.

Patients and methods: This cross-sectional study was conducted in the Department of Nephrology of Sandman Provincial Hospital Quetta from 01-6-2019 till 01-9-2019. A total of 120 patients (52 PPI users and 68 non-PPI users) who were on HD for more than 06 months were included. Data regarding age, gender, duration of hemodialysis and taking PPIs were collected. Determination of serum magnesium was made by taking 3 different samples at 2 weeks' interval and the mean value of serum magnesium was calculated. Serum Mg^{2+} levels <2.0 mg/dL was taken as hypomagnesemia. A Chi-square test was applied to determine the association of PPI use with hypomagnesemia.

Results: Demographic variables such as age and gender were not significantly different between the groups. There was female dominance in both groups (73% in PPI groups and 66.1% in the non-PPI group (p-value 0.65). The mean duration of dialysis was 45.3±13.8 months in PPI users versus 48.9±12.9 months in non-PPI users (p-value 0.14). There was a significantly higher frequency of hypomagnesemia in PPI users; 36 (69.3%) versus 27 (39.7%) in non-PPI users (p-value 0.001).

Conclusion: The use of PPI is associated with a significant reduction in serum magnesium levels. So serum magnesium levels should be advised as routine monitoring in patients of hemodialysis taking PPIs.

Keywords:

Hemodialysis; Proton pump inhibitors; Hypomagnesemia

INTRODUCTION

Patients who are on hemodialysis (due to chronic kidney disease or end-stage renal disease) have poor magnesium excretion mechanisms that can lead to hypomagnesemia.[1,2] Body magnesium has a vital role in several biological processes, such as regulation of ion channels, membrane stabilization, protein synthesis, regulation of enzymes activity.[3] Some recent researches have documented hypomagnesemia as a major risk of mortality in hemodialysis patients. Hypomagnesemia can result in bone disorders, atrial fibrillation and sudden cardiac death in these patients.[4] Proton pump inhibitors (PPIs) routinely prescribed to hemodialysis patients. Because the excretion of PPI is by a hepatic route so these drugs can be safely administrated and there is no need for dose adjustment in these patients.[5] In general, PPIs are prescribed improperly to >50% of patients who do not need these.[6] Recent studies have reported that the excessive use of PPI is associated with several absorptive complications such as B12 deficiency, risk of fractures, neurologic complications, hypomagnesemia, higher risk of community-acquired pneumonia, and chronic kidney disease (CKD).[6-11] PPI use and cardiovascular disease (CVD) are very common in hemodialysis patients and CVD is a major cause of death in hemodialysis patients.[4] Although hemodialysis patients also have a higher prevalence of other CVD risk factors such as dyslipidemia, anemia, hypertension, and diabetes mellitus.[12,13] A large multi-country study reported that PPIs are in-judicially prescribed to many hemodialysis patients and this study reported a significant association of PPIs to use with hypomagnesemia.[14]

Because still there is an ongoing debate whether the use of PPI is associated with hypomagnesemia or not, this study aims to compare the frequency of hypomagnesemia in patients of hemodialysis taking PPI with those not taking PPIs.

PATIENTS AND METHODS

A total of 120 patients who were on hemodialysis for more than 06 months were included in this prospective cross-sectional study, from 01-06-2019 to 01-09-2019. The study population included patients presenting in

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Table 1. Demographic information and etiology of ESRD in two groups

Characteristics	PPI Users (*n*=52)	Non-PPI Users (*n*=68)	p-value
Age [mean±SD]	53.6±11.4	51.8±9.5	0.35
Gender (Female)	38 (73.0%)	45 (66.1%)	0.65
Duration of dialysis (months)	45.3±13.8	48.9±12.9	0.14
Etiology of ESRD			
Polycystic kidney disease	05 (9.6%)	08 (11.7%)	0.48
Renal stone disease	07 (13.4%)	11 (16.1%)	
Hypertension	10 (19.2%)	14 (20.6%)	
Glomerulonephritis	06 (11.5%)	09 (13.2%)	
Unknown	17 (32.7%)	21 (30.9%)	
Diabetic nephropathy	07 (13.5%)	05 (7.3%)	

the Department of Nephrology of Sandman Provincial hospital Quetta. Patients with a history of a cardiovascular disease diagnosed on previous medical records and patients with active bleeding, taking a magnesium supplement, or undergoing hemodialysis due to acute kidney injury (AKI) were excluded. Informed consent from patients and ethical approval from the hospital was taken. Data regarding age, gender, duration of hemodialysis and taking PPIs were collected. Patients taking PPI at least from the last 1 month were labeled PPI users. Determination of serum magnesium was made by taking 3 different samples at 2 weeks interval and the mean value of serum magnesium was calculated. All these samples were taken before hemodialysis. Serum Mg^{2+} levels <2.0 mg/dL was taken as hypomagnesemia.

Data were entered into SPSS v23 software. Continuous variables such as age and duration of HEMODIALYSIS were compared using an independent-sample t-test. Chi-square test was used to compare qualitative variables such as gender, etiology and hypomagnesemia between PPI users and non-PPI users. An independent sample t-test was applied to compare mean Mg^{2+} levels between the groups. P-value ≤0.05 was taken as cut off for significance.

RESULTS

Demographic variables such as age and gender were not significantly different between the groups. The mean age was 53.6±11.4 years in PPI users and 51.8±9.5 years in non-PPI users (p-value 0.35). There was female dominance in both groups (38 (73%) in PPI groups and 45 (66.1%) in the non-PPI group (p=0.65). The mean duration of dialysis was 45.3±13.8 months in PPI users versus 48.9±12.9 months in non-PPI users (p=0.14). There was also no difference in the etiology of ESRD between the groups, in many patients' etiology was unknown in followed by hypertension in both groups. Details are given in Table 1. Mean Mg^{2+} levels were 1.27±0.39 mg/dL in PPI users versus 2.60±0.30 mg/dL in non-PPI group (p-value<0.0001). There was a significantly higher frequency of hypomagnesemia in PPI users; 36 (69.3%) versus 27 (39.7%) in non-PPI users (p=0.001) (Table 2).

DISCUSSION

Magnesium balance is the human body is regulated by three main systems: gastrointestinal, skeletal and renal system. If oral intake of magnesium is decreased, GIT absorption is increased and renal excretion is decreased to main normal magnesium levels if the kidneys are functioning normally. The reverse happens in increased oral intake. Hypo and hypermagnesemia may occur due to a variety of reasons. Some researchers have reported that the use of PPIs in hemodialysis patients is a risk factor of hypomagnesemia in hemodialysis patients.[15] This study found a higher frequency of hypomagnesemia among PPI users (69.3%) in comparison to non-PPI users (39.7%). A possible reason for low magnesium may be because of the loss of Magnesium in the GI system due to PPI use, and it remains subclinical in many patients until symptoms of hypomagnesemia become prominent. Recently some studies have reported that the use of PPI may result in hypomagnesemia in hemodialysis patients. A study conducted by Misra and coauthors found hypomagnesemia in 79% of patients taking PPIs versus in only 43% not taking PPIs, on hemodialysis patients.[16] Nakashima and coworkers reported hypomagnesemia in 11.2% of patients taking PPI and in 5.7% of patients who were not taking any ant-acids.[5] Similar results were reported by other authors.[17,18]

Few researchers have tried to determine the mechanism of hypomagnesemia in patients taking PPI. One study reported low urine levels of magnesium in PPI patients.[19] One more study has reported lower excretion of magnesium in patients taking PPI.[20] A recent study by Bai and colleagues demonstrated that PPI use does

Table 2. Comparison of hypomagnesemia in PPI versus non-PPI users

Characteristics	PPI users (*n*=52)	Non-PPI users (*n* =68)	p-value
Mg^{2+} levels [mean+SD]	1.27±0.39	2.60±0.30	<0.0001
Hypomagnesemia			
Yes	36 (69.3%)	27 (39.7%)	0.001
No	16 (30.7%)	41 (60.3%)	

not affect renal excretion of magnesium but it affects the absorption of magnesium in GIT that results in hypomagnesemia.[21] Lameris and group measured serum magnesium levels in patients taking omeprazole. The authors reported that omeprazole does not affect serum magnesium concentrations.[22] Moreover, GIT diseases such as gastritis, GIT ulcers and GIT reflux are more prevalent in hemodialysis patients as compared to the general population, the prevalence of these has been reported in 70% to 90% hemodialysis patients. This is the reason for the higher use of PPI in hemodialysis patients.[23, 24] Previous studies have reported that duration of PPI is directly related to hypomagnesemia, whereas Hess and associates reported that short duration (14 days) use of PPI can also induce hypomagnesemia.[25] Limitations of the present study include being a cross-sectional study the cause of hypomagnesemia in hemodialysis patients taking PPIs was not determined. Secondly, the length of PPI use was not available. All study patients were taking PPI for more than 1 month. There is a need to conduct studies to determine the cause-and-effect relationship between PPI use and hypomagnesemia.

CONCLUSIONS

The use of PPIs is associated with a significant reduction in serum magnesium levels. Frequent estimation of serum magnesium levels should be advised as routine monitoring in patients of hemodialysis taking PPIs.

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